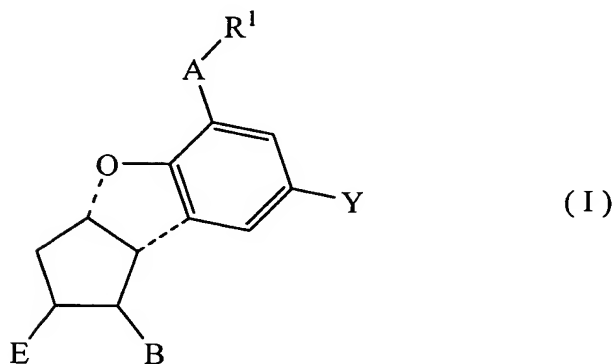


## CLAIMS

1. An enhancing agent for enhancing therapeutic or prophylactic effect of administering (a) renin-angiotensin system inhibitor(s) on (a) renal disease(s), comprising as an effective ingredient a prostaglandin I derivative represented by the Formula (I):



[wherein R<sup>1</sup> is

(A) COOR<sup>2</sup>, wherein R<sup>2</sup> is

hydrogen or a pharmaceutically acceptable cation,

2) C<sub>1</sub>-C<sub>12</sub> straight alkyl or C<sub>3</sub>-C<sub>14</sub> branched alkyl,

Z-R<sup>3</sup>, wherein Z is covalent bond, or straight or branched alkylene represented by C<sub>t</sub>H<sub>2t</sub> wherein t is an integer of 1 to 6, R<sup>3</sup> is C<sub>3</sub>-C<sub>12</sub> cycloalkyl or C<sub>3</sub>-C<sub>12</sub> cycloalkyl substituted with 1 to 3 R<sup>4</sup>(s) wherein R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>5</sub> alkyl,

-(CH<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>CH<sub>3</sub>, wherein n is an integer of 1 to 5,

-Z-Ar<sup>1</sup>, wherein Z represents the same meanings described above, Ar<sup>1</sup> is phenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl, β-thienyl or substituted phenyl (wherein the substituent(s) is(are) at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, C<sub>1</sub>-C<sub>4</sub> alkyl, nitro, cyano, methoxy, phenyl, phenoxy, p-acetamidebenzamide, -CH=N-NH-C(=O)-NH<sub>2</sub>, -NH-C(=O)-Ph, -NH-C(=O)-CH<sub>3</sub> and -NH-C(=O)-NH<sub>2</sub>),

-C<sub>t</sub>H<sub>2t</sub>COOR<sup>4</sup>, wherein C<sub>t</sub>H<sub>2t</sub> and R<sup>4</sup> represent the same meanings as described above,

$-C_tH_{2t}N(R^4)_2$ , wherein  $C_tH_{2t}$  and  $R^4$  represent the same meanings as described above,  
 $-CH(R^5)-C(=O)-R^6$ , wherein  $R^5$  is hydrogen or benzoyl, and  $R^6$  is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidephenyl or 2-naphthyl,

5  $-C_pH_{2p}-W-R^7$ , wherein W is  $-CH=CH-$ ,  $-CH=CR^7-$  or  $-C\equiv C-$ , wherein  $R^7$  is hydrogen,  $C_1-C_{30}$  straight or branched alkyl or  $C_1-C_{30}$  aralkyl, p is an integer of 1 to 5, or

10)  $-CH(CH_2OR^8)_2$ , wherein  $R^8$  is  $C_1-C_{30}$  alkyl or acyl,

(B)  $-CH_2OH$ ,

10 (C)  $-C(=O)N(R^9)_2$ , wherein  $R^9$  is hydrogen,  $C_1-C_{12}$  straight alkyl,  $C_3-C_{12}$  branched alkyl,  $C_3-C_{12}$  cycloalkyl,  $C_4-C_{13}$  cycloalkylalkylene, phenyl, substituted phenyl (wherein the definitions of the substituent(s) are the same as those described in (A) 5) mentioned above),  $C_7-C_{12}$  aralkyl or  $-SO_2R^{10}$  wherein  $R^{10}$  is  $C_1-C_{10}$  alkyl,  $C_3-C_{12}$  cycloalkyl, phenyl, substituted phenyl (wherein the definition(s) of the

15 substituent(s) is(are) the same as those described in (A) 5) mentioned above), or  $C_7-C_{12}$  aralkyl, wherein the two  $R^9$ s may be the same or different, with the proviso that when one of them is  $-SO_2R^{10}$ , the other  $R^9$  is not  $-SO_2R^{10}$ , or

(D)  $-CH_2OTHP$  (wherein THP is tetrahydropyranyl),

A is

20  $-(CH_2)_m-$ ,

$-CH=CH-CH_2-$ ,

$-CH_2-CH=CH-$ ,

$-CH_2-O-CH_2-$ ,

$-CH=CH-$ ,

25  $-O-CH_2-$  or

7)  $-C\equiv C-$ , wherein m is an integer of 1 to 3,

Y is hydrogen,  $C_1-C_4$  alkyl, chlorine, bromine, fluorine, formyl, methoxy or nitro,

B is  $-X-C(R^{11})(R^{12})OR^{13}$ , wherein  $R^{11}$  is hydrogen or  $C_1$ - $C_4$  alkyl,  $R^{13}$  is hydrogen,  $C_1$ - $C_{14}$  acyl,  $C_6$ - $C_{15}$  aroyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl or t-butyl,

X is

- 5      $-CH_2-CH_2-$   
         $-CH=CH-$  or  
         $-C\equiv C-$ ,

$R^{12}$  is

$C_1$ - $C_{12}$  straight alkyl,  $C_3$ - $C_{14}$  branched alkyl,

- 10     $-Z-Ar^2$ , wherein Z represents the same meanings as described above,  $Ar^2$  is phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, or phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl,  $C_1$ - $C_4$  alkyl, nitro, cyano, methoxy, phenyl and phenoxy,

- 15     $-C_tH_{2t}OR^{14}$ , wherein  $C_tH_{2t}$  represents the same meanings as described above,  $R^{14}$  is  $C_1$ - $C_6$  straight alkyl,  $C_3$ - $C_6$  branched alkyl, phenyl, phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl,  $C_1$ - $C_4$  alkyl, nitro, cyano, methoxy, phenyl or phenoxy-substituted phenyl, cyclopentyl, cyclohexyl, cyclopentyl substituted with 1 to 4  $C_1$ - $C_4$  straight alkyl and cyclohexyl substituted with 1 to 4  $C_1$ - $C_4$  straight alkyl,

- 20     $-Z-R^3$ , wherein Z and  $R^3$  represent the same meanings as mentioned above,  
         $-C_tH_{2t}-CH=C(R^{15})R^{16}$ , wherein  $C_tH_{2t}$  represents the same meanings as mentioned above,  $R^{15}$  and  $R^{16}$  represent hydrogen, methyl, ethyl, propyl or butyl, or

6)      $-C_uH_{2u}-C\equiv C-R^{17}$ , wherein u is an integer of 1 to 7,  $C_uH_{2u}$  is straight or branched alkylene, and  $R^{17}$  is  $C_1$ - $C_6$  straight alkyl,

- 25    E is hydrogen or  $-OR^{18}$ , wherein  $R^{18}$  is  $C_1$ - $C_{12}$  acyl,  $C_7$ - $C_{15}$  aroyl or  $R^2$  (wherein  $R^2$  represents the same meanings as described above),

said formula includes d-isomers, l-isomers and racemic compounds].

2. The enhancing agent according to claim 1, wherein in said Formula (I),  
 $R^1$  is  $\text{COOR}^2$ ,

wherein  $R^2$  is hydrogen or a pharmaceutically acceptable cation,

A is

- 5           1)  $-(\text{CH}_2)_m-$   
              2)  $-\text{CH}_2-\text{CH}=\text{CH}-$

wherein m is an integer of 1 to 3,

Y is hydrogen,

B is  $-\text{X}-\text{C}(\text{R}^{11})(\text{R}^{12})\text{OR}^{13}$ ,

10           wherein  $\text{R}^{11}$  and  $\text{R}^{13}$  is hydrogen, X is

- 1)  $-\text{CH}=\text{CH}-$   
              2)  $-\text{C}\equiv\text{C}-$ ,

$\text{R}^{12}$  is

- 1)  $-\text{Z}-\text{Ar}^2$

15           wherein Z is covalent bond, or straight or branched alkylene represented  
 by  $\text{C}_t\text{H}_{2t}$  wherein t is an integer of 1 to 6,  $\text{Ar}^2$  is phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, or  
 phenyl substituted with at least one of chlorine, bromine, fluorine, iodine,  
 trifluoromethyl,  $\text{C}_1$ - $\text{C}_4$  alkyl, nitro, cyano, methoxy, phenyl and phenoxy, or

- 2)  $-\text{Z}-\text{R}^3$

20           wherein Z represents the same meanings as described above,  $\text{R}^3$  is  $\text{C}_3$ - $\text{C}_{12}$   
 cycloalkyl, or

- 3)  $-\text{C}_u\text{H}_{2u}-\text{C}\equiv\text{C}-\text{R}^{17}$

wherein u is an integer of 1 to 7,  $\text{C}_u\text{H}_{2u}$  is straight or branched alkylene,  
 and  $\text{R}^{17}$  is  $\text{C}_1$ - $\text{C}_6$  straight alkyl,

25           said formula includes d-isomers, l-isomers and racemic compounds.

3. The enhancing agent according to claim 1, wherein in said Formula (I),  
 $\text{R}^1$  is  $\text{COOR}^2$ , wherein  $\text{R}^2$  is hydrogen or a pharmaceutically acceptable cation,

A is  $-(CH_2)_m-$ , wherein m is an integer of 1 to 3,

Y is hydrogen,

B is  $-X-C(R^{11})(R^{12})OR^{13}$ , wherein  $R^{11}$  and  $R^{13}$  is hydrogen,

X is  $-CH=CH-$ ,

5  $R^{12}$  is  $-C_uH_{2u}-C\equiv C-R^{17}$ , wherein u is an integer of 1 to 7,  $C_uH_{2u}$  is straight or branched alkylene, and  $R^{17}$  is  $C_1-C_6$  straight alkyl,

E is hydrogen or  $-OR^{18}$ , wherein  $R^{18}$  is  $R^2$  (wherein  $R^2$  represents the same meanings as described above),

said formula includes d-isomers, l-isomers and racemic compounds.

- 10 4. The enhancing agent according to claim 1, wherein said prostaglandin I derivative is beraprost or pharmaceutically acceptable salt or ester thereof.
5. The enhancing agent according to any one of claims 1 to 4, wherein said renin-angiotensin system inhibitor is an ACE inhibitor.
6. The enhancing agent according to claim 5, wherein said ACE inhibitor is  
15 selected from the group consisting of enalapril maleate, alacepril, delapril, ramipril, captopril, lisinopril, benazepril hydrochloride, libenzapril, quinaprilat, imidapril hydrochloride, zofenopril calcium, fosinopril sodium, cilazapril, temocapril hydrochloride, spirapril hydrochloride, perindopril erbumine, moexipril hydrochloride, trandolapril, ceronapril hydrate, utibapril, omapatrilat, Sampatrilat,  
20 and their pharmaceutically acceptable salts.
7. The enhancing agent according to any one of claims 1 to 4, wherein said renin-angiotensin system inhibitory substance is a compound having antagonistic action against angiotensin II receptor.
8. The enhancing agent according to claim 7, wherein said compound having  
25 antagonistic action against angiotensin II receptor is selected from the group consisting of losartan, eprosartan, candesartan cilexetil, valsartan, telmisartan, irbesartan, tasosartan, olmesartan medoxomil, EXP-3174, zolasartan, saprisartan,

elisartan potassium, ripisartan, milfasartan, forasartan, embusartan, fonsartan, E4177, YM358, ICI-D8731, TAK-536, CL-329167, pomisartan, candesartan, and their pharmaceutically acceptable salts.

9. The enhancing agent according to claim 8, wherein said compound having  
5 antagonistic action against angiotensin II receptor is selected from the group  
consisting of losartan, eprosartan, candesartan cilexetil, valsartan, telmisartan,  
irbesartan, tasosartan, olmesartan medoxomil, EXP-3174, zolasartan, saprisartan,  
embusartan, candesartan, and their pharmaceutically acceptable salts.

10. The enhancing agent according to any one of claims 1 to 9, wherein said renal  
10 disease is diabetic nephropathy, glomerulonephritis, interstitial nephritis, acute renal  
failure, or chronic renal failure.

11. The enhancing agent according to claim 9, wherein said renal disease is  
chronic renal failure.

12. The enhancing agent according to any one of claims 1 to 11, wherein said  
15 effect of administering renin-angiotensin system inhibitor is the effect to suppress  
elevation of serum creatinine with time during said renal disease(s).

13. The enhancing agent according to any one of claims 1 to 11, wherein said  
effect of administering renin-angiotensin system inhibitory substance is the effect to  
suppress sequential decrease in the reciprocal of serum creatinine with time.

20 14. The enhancing agent according to any one of claims 1 to 11, wherein said  
effect of administering renin-angiotensin system inhibitor is the effect to suppress  
decrease in the glomerular filtration rate with time during said renal disease(s).

15. A therapeutic or prophylactic agent for renal disease, comprising as effective  
ingredients the enhancing agent according to any one of claims 1 to 14 and a renin-  
25 angiotensin system inhibitor.

16. A kit for therapy or prophylaxis for renal diseases, comprising separately the  
enhancing agent according to any one of claims 1 to 14, and a drug containing as an

effective ingredient a renin-angiotensin system inhibitor, wherein said kit is for administering the enhancing agent and the renin-angiotensin system inhibitor at the same time or at different times.

5 17. A method for enhancing therapeutic or prophylactic effect of renin-angiotensin system inhibitor on renal disease, comprising administering the enhancing agent according to any one of claims 1 to 14 to a patient to whom (a) rennin-angiotensin system inhibitor(s) is(are) administered.

10 18. A method for treating or preventing a renal disease, comprising administering said therapeutic or prophylactic agent for renal diseases according to claim 15, or the drugs contained in the kit of therapeutic or prophylactic agents for renal diseases according to claim 16.

19. Use of said prostaglandin I derivative recited in any one of claims 1 to 4, for the production of an agent for enhancing the therapeutic or prophylactic effect of administering the renin-angiotensin system inhibitor on renal diseases.

15 20. The use according to claim 19, wherein said enhancing agent is the enhancing agent according to any one of claims 5 to 14.